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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of

Filippo BELARDELLI et al. Conf. 1462

Application No. 09/845,042 Group 1644

Filed April 27, 2001 Examiner Gerald R Ewoldt

METHOD FOR GENERATING HIGHLY ACTIVE HUMAN DENDRITIC CELLS FROM MONOCYTES

APPEAL BRIEF

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(i) Real Party in Interest

The real party in interest in this appeal is the assignee, Istituto Superiore di Sanita, of Rome, Italy.

(ii) Related Appeals and Interferences

None.

(iii) Status of Claims

Claims 54, 55, 57, 58, 61-63, 66, 67 and 69-83 are pending. Claims 82 and 83 were withdrawn from consideration. The present appeal is taken from the final rejection of claims 54, 55, 57, 58, 61-63, 66, 67 and 69-81.

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(iv) Status of Amendments

An Amendment After Final Rejection filed simultaneously herewith corrects two obvious errors in claim dependency and two other obvious typographical errors, thereby to obviate the indefiniteness rejection applied at Item 8 of the final rejection and to permit the present appeal to focus solely on the substantive issues.

(v) Summary of the Claimed Subject Matter

The claimed invention is a method for producing dendritic cells from human mononuclear cells. As discussed in the present specification for example at page 1, lines 18-21, dendritic cells are recognized for their antigen-presenting capability, and thus play a key role in priming the immune response. However, as discussed at page 3, lines 18-23 of the specification, the therapeutic use of dendritic cells has been limited by their low occurrence in peripheral blood and the difficulty of harvesting them from bone marrow and lymphoid tissue.

The invention improves upon techniques for producing dendritic cells from human mononuclear cells, e.g. peripheral blood monocytes. That is, previous researchers have shown that it is possible to make dendritic cells by

culturing a patient's monocytes *ex vivo* under selected culturing conditions, which results in the transformation ("differentiation") of the cells into a distinct phenotype, namely that of immature dendritic cells (page 3, line 24 - page 4, line 24).

The present inventors have discovered that such dendritic cells can be made more rapidly and in a single step by differentiating the mononuclear cells in the presence granulyte/monocyte colony-stimulating factor (GM-CSF) and type I interferon gamma (IFN), for up to three days (page 5, line 9-14 and line 28-32).

The independent claims 54, 63, 69 and 72 each reflect that discovery, and claim the invention in somewhat different ways, particularly as regards the amounts of type I IFN and GM-CSF to be used in the culture.

(vi) Grounds of Rejection to be Reviewed on Appeal

There are two issues on appeal, namely:

1) Whether the claims on appeal are supported by an enabling disclosure; and

2) Whether the claims on appeal contain new matter.

The claims on appeal are recognized as being free of the prior art of record.

(vii) Argument

The claims are supported by an enabling disclosure

The final rejection notes that the examples described in the specification utilize concentrations of 1000 U/ml for the type I IFN, and 500 IU/ml for the GM-CSF. The final rejection contends that these illustrations of preferred embodiments of the invention are somehow evidence that the claims are not enabled for the recited concentration ranges of type I IFN and GM-CSF, which, in their broadest versions now claimed, are 400 to 10,000 IU/ml for type I IFN and 250-1,000 IU/ml for GM-CSF (claims 54 and 72).

The final rejection moreover acknowledges evidence of record that the invention has subsequently been shown to work at a type I IFN concentration of 500 IU/ml.

What is conspicuously lacking in the final rejection is any evidence or reasoning to support a belief that any claim on appeal would be inoperable over any portion, much less a substantial portion, of the recited concentration ranges. It is of course well-settled that the Patent Office bears the burden as to this:

> Any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen et al*, 492 F.2d 856, 858; 181 USPQ 46 (CCPA 1974).

Here, the final rejection makes no attempt to carry that burden, but instead seeks improperly to shift it to appellants. The only purported justification is the one-word characterization of the invention as "unexpected," which is true of the invention in relation to the prior art, but does not bear on the presumed enablement of what is taught in the specification itself.

Consequently, it is believed to be apparent that the non-enablement rejection is improper as a matter of law and should be reversed.

None of the claims contains new matter

The final rejection at pages 4-5 identifies the following claim recitations as allegedly being new matter:

1. "in the absence of IL-4" (claims 54, 63 and 69);

2. "for a maximum of three days" (claims 54, 63, 69 and 72);

3. "collecting cells within three days" (claim 69);

4. "within three days" (claims 72-76);

5. "500-10,000 IU/ml [of type I IFN]" (claim 57 and 63);

6. "500-1,000 IU/ml [of GM-CSF]" (claims 61 and 63); and

7. TM-CSF (claim 75) and CM-CSF (claims 79-81).

Item 7 on the above list are the two obvious typographical errors corrected by the amendment filed simultaneously herewith, and should never have been included in a new matter rejection.

That the method of claims 54, 63 and 69 is performed "in the absence of IL-4" is well-supported by the disclosure appearing for example at pages 19-39 of the specification. There, dendritic cells according to the invention, prepared in the presence of IFN and GM-CSF ("IFN-DCs"), are thoroughly compared and contrasted with dendritic cells prepared in the presence of interleukin 4 (IL-4) and GM-CSF ("IL-4-DCs"). It is therefore clear that the process of the invention is performed in the absence of IL-4. This is further supported by the examples described at pages 16-17, where the detailed description of the culturing conditions for the IFN-DCs omits any mention of IL-4, confirming its absence.

The maximum three day culture time is likewise abundantly supported by the specification as filed. It will be recalled that the specification at page 3, line 24 - page 4, line 24 discusses several prior art processes, in which the culture time was 5-7 days. Then, in the summary of the present invention, the specification teaches at page 5, lines

5 and 20 that a "rapid generation" and a "particularly rapid procedure" are provided.

The specification goes on to teach explicitly at page 5, lines 28-32 that the process is preferably carried out "within three days of culture," and the three-day culture is mentioned repeatedly throughout the specification, for example at page 9, lines 29 and 32-33; Page 10, lines 3 and 20; page 11, line 20; page 12, lines 1, 7, 22 and 29-30; page 14, line 1; page 15, lines 12-13; page 18, lines 16-18 and 19-20; page 26, lines 6-8 and page 28, line 30.

These passages clearly support the recitations of "for a maximum of three days," "collecting cells within three days," and "within three days" (claims 72-76) that appear in the claims on appeal.

It is noteworthy that the term "maximum" was introduced by amendment because the recitation of culturing for three days was considered in a previous official action to read on the longer 5-7 day culture times of the prior art. Upon amending the claims as supported by the disclosure to avoid that overbroad reading, the present new matter rejection was then applied. However, that rejection is seen to be ill-conceived; three days is not four days, neither is it five or seven. Even if the specification were considered to teach

longer culture times than three days, a maximum of three days is clearly a preferred embodiment as supported by the many passages quoted above, and appellants are entitled to claim it.

As to the concentration range of "500-10,000 IU/ml" of type I IFN in claims 57 and 63, this is clearly adequately supported by the specification for example at page 6, lines 8-12. The explicit disclosure of preferred ranges of 400-10,000 IU/ml and 500-2,000 IU/ml in that passage of the specification unquestionably supports the recited range of 500-10,000 IU/ml. See, e.g., *In re Wertheim et al*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976).

Lastly, as to the concentration range of "500-1,000 IU/ml" of GM-CSF in claims 61 and 63, the same result obtains from a consideration of page 5, lines 33-34, where a range of 250-1,000 IU/ml is taught, in conjunction with, for example, page 10, lines 19-20, where a particularly preferred concentration of 500 IU/ml of GM-CSF is described. The *Wertheim* case identified above likewise compels the conclusion that this range is not new matter.

The above discussion is believed to show that none of the bases of the new matter rejection is well-founded, and that the rejection should be reversed in its entirety.

Conclusion

From the foregoing, it is believed to be apparent that neither the non-enablement rejection nor the new matter rejection merits affirmance by the Board, but rather that both rejections should be reversed. Such action is accordingly respectfully requested.

Respectfully submitted,

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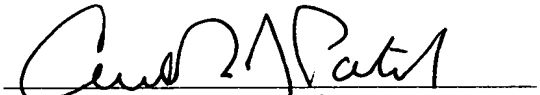
By 

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(viii) Claims Appendix

54. A process for deriving dendritic cells from mononuclear cells in culture wherein said mononuclear cells are peripheral blood mononuclear cells (PBMC) or CD14+ monocytes, comprising culturing said mononuclear cells for a maximum of three days with type I interferon (IFN) at a concentration of 400 to 10,000 IU/ml in the presence of GM-CSF at a range of 250-1,000 IU/ml, and in the absence of IL-4, and recovering dendritic cells from said culture.

55. The process according to claim 54, wherein said type I IFN is selected from the group consisting of natural IFN-alpha, recombinant species of IFN-alpha, natural IFN-beta, recombinant IFN-beta and consensus IFN α (CIFN).

57. The process according to claim 54, wherein type I IFN is present in the culture medium at a concentration in a range of 500-10,000 IU/ml.

58. The process according to claim 57, wherein type I IFN is present in the culture medium at a concentration of 1,000 IU/ml.

61. The process according to claim 54, wherein said GM-CSF is at a concentration in a range of 500-1,000 IU/ml.

62. The process according to claim 54, further comprises contacting dendritic cells, obtained by treating mononuclear cells with type I-IFN, with a maturation agent selected from the group consisting of bacterial extract, poly-IC and CD40 ligand.

63. A method for the ex vivo derivation of dendritic cells from mononuclear cells within 3 days of culture, wherein said mononuclear cells are peripheral blood mononuclear cells (PBMC) or CD14+ monocytes, comprising culturing type I IFN for a maximum of 3 days with said mononuclear cells from the beginning of said culture at a concentration range of 500 to 10,000 IU/ml, in the presence of GM-CSF at a concentration in a range of 500-1,000 IU/ml, and in the absence of IL-4.

66. The method according to claim 63, wherein said type IFN concentration is in a range of 500-2,000 IU/ml.

67. The method according to claim 66, wherein said type I IFN concentration is 1,000 IU/ml.

69. A method for the ex vivo derivation of dendritic cells from mononuclear cells, wherein said mononuclear cells are isolated peripheral blood mononuclear cells (PBMC) or isolated CD14+ monocytes, comprising culturing said isolated peripheral blood mononuclear cells (PBMC) or isolated CD14+ monocytes for a maximum of 3 days in a culture with type I IFN at a concentration 400-10,000 IU/ml and GM-CSF in a concentration of 250-1,000 IU/ml and in the absence of added IL-4, and collecting said cells within 3 days of culture.

70. The method according to claim 69, wherein said type I IFN concentration is in a range of 500-10,000 IU/ml.

71. The method according to claim 70, wherein said type I IFN concentration is in a range of 500-1,000 IU/ml.

72. A process for producing dendritic cells from mononuclear cells wherein said mononuclear cells are peripheral blood mononuclear cells (PBMC) or CD14+ monocytes,

comprising culturing said mononuclear cells for a maximum of 3 days with type I interferon (IFN) at a concentration in the range of 400-10,000 IU/ml in the presence of GM-CSF at a concentration in a range of 250-1,000 IU/ml, and wherein said dendritic cells express higher levels of CD83 and CD25 antigens as compared to mononuclear cells or monocytes that have been cultured within 3 days of treatment with GM-CSF and IL-4.

73. The process according to claim 72, wherein levels of CD40, CD54, CD80, CD86 and HLA-DR molecules are in higher levels as compared to mononuclear cells of monocytes treated with IL-4 and GM-CSF within 3 days of culture.

74. The process according to claim 72, wherein said dendritic cells express high levels of IP-10 and IL-15 as compared to mononuclear cells or monocytes within 3 days of culture that are treated with IL-4 and GM-CSF.

75. The process according to claim 72, wherein an early detachment monocytes from the culture plates occurs during said process, and said dendritic cells exhibit high levels of CD40, CD54, CD80, CD86 and HLA-DR molecules as

compared to mononuclear cells or monocytes within 3 days of culture with IL-4 and GM-CSF; wherein said dendritic cells express higher levels of CD83 and CD25 as compared to mononuclear cells or monocytes within 3 days of culture with IL-4 and GM-CSF; and wherein CD123 is more expressed in said dendritic cells as compared to mononuclear cells or monocytes that have been treated for 3 days with GM-CSF and IL-4.

76. The process according to claim 72, wherein said dendritic cells express higher levels of HLA-DR as compared to mononuclear cells or monocytes that have been cultured within 3 days of treatment with GM-CSF and IL-4.

77. The process according to claim 72, wherein said dendritic cells retain a dendritic cell phenotype without adhering to a plastic surface, whereas monocyte cells or monocytes treated with IL-4 and GM-CSF for 3 days re-acquire macrophage characteristics and re-adhere to culture flasks, unless stimulated to terminally differentiate.

78. The process according to claim 73, wherein said mononuclear cells or monocytes cultured with IL-4 and

GM-CSF are cultured with 500 U/ml of CM-CSF and 500 U/ml of IL-4.

79. The process according to claim 74, wherein said mononuclear cells or monocytes cultured with IL-4 and GM-CSF are cultured with 500 U/ml of GM-CSF and 500 U/ml of IL-4.

80. The process according to claim 75, wherein said mononuclear cells or monocytes cultured with IL-4 and GM-CSF are cultured with 500 U/ml of GM-CSF and 500 U/ml of IL-4.

81. The process according to claim 76, wherein said mononuclear cells or monocytes cultured with IL-4 and GM-CSF are cultured with 500 U/ml of GM-CSF and 500 U/ml of IL-4.

(ix) Evidence Appendix

None.

(x) Related Proceedings Appendix

None.